Automated electroencephalographic discontinuity in cooled newborns predicts cerebral MRI and neurodevelopmental outcome

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Short title: EEG discontinuity in cooled newborns

Key words: EEG, discontinuity, MRI, neurodevelopment, therapeutic hypothermia

Abbreviations: TH – therapeutic hypothermia

Financial disclosure statement: The authors have no financial relationships relevant to this article to disclose.

Funding source: JPB received funding support from Theirworld

Potential conflicts of interest: None

What is known about this topic:
EEG discontinuity is associated with adverse neurologic outcomes in term infants after hypoxic-ischaemic encephalopathy.

What this study adds:
In term infants receiving therapeutic hypothermia, EEG discontinuity calculated using a novel algorithm at 24 hours is associated with cerebral tissue injury on MRI and with adverse neurodevelopmental outcomes. Therefore, it may provide a useful tool for early risk stratification when adjunctive therapies are most beneficial.

Contributors' Statement:

Jonathan M Dunne collected data, carried out the raw EEG data analysis, assisted with the statistical analysis, wrote the first draft of the manuscript and approved the final version of the manuscript.

David Wertheim developed the EEG software used to measure discontinuity, assisted with writing the manuscript and approved of the final version of the manuscript.

Paul Clarke, obtained ethics approval, collected data, assisted with writing the manuscript and approved the final version of the manuscript.

Olga Kapellou reviewed the MR images and approved of the final version of the manuscript.

Philippa Chisholm carried out neurodevelopmental testing and approved the final version of the manuscript.

James P Boardman reviewed the MR images, assisted with writing the first draft of the manuscript, assisted with statistical analysis and approved the final version of the manuscript.

Divyen K Shah conceived the study, collected data, assisted with the EEG reviews, statistical analysis, writing the first draft of the manuscript, approved of the final version of the manuscript and is guarantor.

Word Count: 2498

Abstract

Background and Hypothesis: Prolonged EEG discontinuity has been associated with poor neurodevelopmental outcomes after perinatal asphyxia but its predictive value in the era of therapeutic hypothermia (TH) is unknown. Hypothesis: In infants undergoing TH for hypoxic-ischaemic encephalopathy (HIE) prolonged EEG discontinuity is associated with cerebral tissue injury on MRI and adverse neurodevelopmental outcome.

Method: Retrospective study of term neonates from 3 UK centres who received TH for perinatal asphyxia, had continuous 2 channel aEEG with EEG for a minimum of 48 hours, brain MRI within 6 weeks of birth, and neurodevelopmental outcome data at a median age of 24 months. Mean discontinuity was calculated utilising a novel automated algorithm designed for analysis of the raw EEG signal.

Results: Of 49 eligible infants, 17 (35%) had MR images predictive of death or severe neurodisability (unfavourable outcome) and 29 (59%) infants had electrographic seizures. In multivariable logistic regression, mean discontinuity at 24 hours and 48 hours (both $p=0.01$), and high seizure burden ($p=0.05$) were associated with severe cerebral tissue injury on MRI. A mean discontinuity >30s per minute-long epoch, had a specificity and positive predictive value of 100%, sensitivity of 71% and a negative predictive value of 88% for unfavourable neurodevelopmental outcome at a 10μV threshold.

Conclusions: In addition to seizure burden, excessive EEG discontinuity is associated with increased cerebral tissue injury on MRI and is predictive of abnormal neurodevelopmental outcome in infants treated with TH. The high positive predictive value of EEG discontinuity at 24 hours may be valuable in selecting newborns with HIE for adjunctive treatments.

Introduction

Hypoxic-ischaemic encephalopathy (HIE) affects up to 6 per 1000 live births in industrialised nations and is an important cause of disability in survivors[1 2]. Mild therapeutic hypothermia (TH) is a safe and effective neuroprotective intervention and is now standard care in resource-rich settings[3 4]. TH increases the number of survivors without neurodisability, with the benefits persisting into childhood[5]. The number needed to treat is nine[4], so there is a need to stratify patients who may stand to benefit from adjunctive therapies, and to improve the precision of prognostic information for families and clinicians.

In the precooling era, prolonged EEG discontinuity of 30s or longer in term newborns with HIE[6], as well as in other conditions including cerebral haemorrhage and infection[7], was associated with unfavourable neurodevelopmental outcomes. However, the applicability of EEG quantification for infants undergoing TH after HIE is unclear. Continuous limited channel EEG with amplitude-integrated EEG (aEEG) monitoring is routinely used at the bedside in newborns undergoing TH for assessment of electrocortical background and to screen for seizures[8]. We have previously shown that electrographic seizure burden is independently associated with cerebral tissue injury on MRI in term-born infants undergoing TH[8].

Severely abnormal EEG and aEEG background patterns are associated with adverse outcome[9 10], but the precise features of the background that predict poor outcome are uncertain and qualitative assessments lack diagnostic precision and are susceptible to inter-observer variation. In order to improve the objectivity of EEG assessment in the newborn, we developed and applied computer software for automated quantification of EEG discontinuity.

We aimed to test the hypothesis that an objective measure of EEG discontinuity is associated with cerebral tissue injury on MRI and neurodevelopmental outcome.

Method

We studied infants who received TH between October 2007 and July 2011 in three tertiary UK Neonatal Intensive Care Units (NICUs): the Royal London Hospital, Homerton University Hospital, and Norfolk and Norwich University Hospital. Data were obtained as part of standard clinical care. This study had Research Ethics Committee approval (UK REC reference 14/EE/0205).

Subjects

Neonates were eligible for inclusion if they were born at ≥36 weeks' gestation, treated with whole body TH for moderate to severe HIE (defined using standard criteria)[11], had aEEG monitoring within 12 hours of birth, and had brain MRI within 6 weeks. Exclusion criteria included death prior to MR imaging, images degraded by motion artefact, major congenital anomaly or a primary diagnosis of an inborn error of metabolism. The cohort is a subset of a larger cohort reported previously[8].

Infants received intensive care and TH according to local guidelines, which were informed by the UK TOBY Cooling Register Clinician's Handbook[12]. Sentinel events were defined as a sustained (pre-terminal) fetal bradycardia necessitating delivery of the infant, antepartum haemorrhage secondary to placental abruption, placenta praevia, cord prolapse or rupture, uterine rupture and shoulder dystocia.

aEEG/EEG monitoring and discontinuity analysis

Recordings obtained from the aEEG monitors (BRM2/3 BrainZ Instruments, Natus Medical Inc., CA, USA) were reviewed off-line (by DS and JD) to visually identify seizure-free and minimum artefact 2-hour epochs at 24 and 48 hours of age. Single channel cross-cerebral (P3-P4) EEG data were exported to Excel, and continuity was analysed in 1-minute epochs using software that we developed using MATLAB (The MathWorks, Inc., MA, USA), similar to that validated in previous work by comparing with visual assessment[13]. The system detected an

interval if the absolute amplitude of the EEG was less than 15 μV with respect to the baseline for at least 6 seconds and therefore discontinuous; the analysis was repeated with a 10 μV threshold. The 10 and 15 μV thresholds were chosen to reflect the fact that the EEG from healthy term newborns is represented by more lower voltage high frequency wave forms in contrast to preterm or encephalopathic infants[14]. For each recording the mean of the total interval length per epoch, the discontinuity value, was calculated and expressed in seconds. For an interval to be detected the minimum period of 6 seconds was chosen in order to avoid including normal short quiescent periods seen in tracé alternant[15]. In order to allow assessment of temporal variability in EEG discontinuity, the length of the analysis epochs was one minute; intervals that started in the preceding epoch and continued into a subsequent period were included in the analysis. EEG discontinuity greater than 30 s per minute was regarded as a predominantly discontinuous trace, as this equates to 50% discontinuity within a minute implying that the EEG is predominantly discontinuous at the given amplitude threshold. This is similar to approaches previously applied in visual assessment of term infant EEG recordings[7]. For four traces, the analysis was repeated which yielded the same mean interval duration.

MR Imaging

Magnetic resonance imaging was performed at local centres with conventional T1-weighted and T2-weighted sequences acquired at 1.5 Tesla. Anonymised images were rated independently by two investigators (OK and JPB), who were blind to the clinical data. The pattern of MRI injury was classified into two groups, using the system described by Rutherford et al.[16], which has prognostic value in the era of TH. This method includes rating the posterior limb of the internal capsule (PLIC), basal ganglia and thalami (BGT) and the subcortical white matter. Group 1 had a severe pattern of injury that predicts poor outcome, defined by the classification system as death or one or more of: mental development index (MDI) score less than 70 (≥2 SD below the mean) on the Bayley Scales of Infant Development (BSID II); score of 3–5 on the gross motor function classification system (GMFCS); or bilateral cortical visual

impairment with no useful vision. Group 2 had either normal images or less severe patterns of injury associated with normal or mildly abnormal (favourable) neurodevelopmental outcome. These patterns of injury were used to assign infants into either the favourable or unfavourable MR images outcome group.

Neurodevelopmental Outcomes

For the purposes of neurodevelopmental outcomes, infants were classified in the unfavourable outcome group if they had cerebral palsy that impaired independent walking; severe seizure disorder; hearing impairment requiring hearing aids or bilateral cortical visual impairment with no useful vision. Infants with better outcomes were placed in the favourable outcome group. Neurodevelopmental outcomes were assessed at multiple local centres, with tools of assessment including both BSID and Griffiths.

Statistical Analysis

Data were analysed using SPSS V22 (IBM). We investigated discontinuity at 10 and 15 μV thresholds at both 24 and 48 hour time epochs, seizure burden, Apgar score at 10 minutes, use of anticonvulsants, worst arterial cord or infant pH and base deficit within the first hour in univariable analyses with cerebral tissues injury on MRI using χ^2 statistic for categorical variables and analysis of variance (ANOVA) for continuous variables. Seizures were classified as previously reported for this cohort[8]. Seizures were defined as rhythmic spike and/or wave activity on the raw EEG lasting at least 10 s in the absence of artefact. A low seizure burden was defined as no seizures or sporadic seizures lasting < 15 minutes in a single hour. A seizure episode lasting ≥ 15 minutes per hour for any hour during the period of monitoring including the cooling and rewarming period was classified as high seizure burden.

Significant factors from the univariable analyses were examined in a binary logistic regression model to calculate odds ratios (OR), assessing their association with MRI outcome. The area under the receiver operating characteristic (ROC) was calculated for the relationship between

discontinuity >30s and unfavourable MRI outcomes. The OR, positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity were calculated for the relationship between discontinuity >30s and unfavourable neurodevelopmental outcomes. Two-sided p values were regarded as significant at the 0.05 threshold.

Results

Of 52 eligible infants, three were excluded due to incomplete EEG recordings at 48 hours. The clinical characteristics of the remaining 49 are described in Table 1 and the EEG discontinuity measures, MRI findings and neurodevelopmental outcomes are detailed in the Table 2.

MRI Outcomes

Seventeen (35%) of the study cohort had MR images predictive of unfavourable outcome.

On univariable analysis, factors associated with the unfavourable pattern of MRI outcome were high seizure burden ($p=0.003$), discontinuity at 24 hours ($p<0.001$) and at 48 hours ($p<0.001$) at 15 μV threshold (Table 3).

In multivariable logistic regression high seizure burden (OR 4.2, 95% CI 1.01–17.48; $p=0.05$), mean discontinuity at 24 hours (OR 1.04, 95% CI 1.01–1.08; $p=0.01$) and at 48 hours (OR 1.05, 95% CI 1.01-1.10; $p=0.01$) were associated with severe cerebral tissue injury on MRI (using the method described by Rutherford et al[16]). Of infants with unfavourable MRI outcomes, the median (IQR) discontinuity in seconds was 31.2 (0.9, 51.8) and 43.5 (8.6, 56.5) at 10 and 15 μV respectively at 24 hours, and 2.7 (0.1, 42.7) and 20.3 (1.9, 53.2) at 48 hours (Figure 1). A mean discontinuity >30 s per 1-minute epoch had a PPV of 90% and 86% at 24 and 48 hours respectively (10 μV threshold) and of 75% and 80% at 24 and 48 hours (15 μV threshold) for group 1 (unfavourable MRI outcome), The area under the ROC curve at both thresholds and both time points was between 0.78 and 0.81 showing a high predictive value for discontinuity at both time points and thresholds. To investigate the possibility of collinearity between seizure burden and discontinuity (24 hours, 10 μV threshold) in the regression model we calculated correlation between these two variables and found the Pearson coefficient to be low, 0.30 ($p=0.036$).

Neurodevelopmental Outcomes

Neurodevelopmental outcomes were available for 43/49 (88%) of the children (Table 2). Median age (interquartile range) of last follow-up was 24 (24, 24) months. 14/43 (33%) children had unfavourable clinical outcomes: four had died, six had cerebral palsy, two required bilateral hearing aids for profound sensori-neural hearing loss, one had autism, seizures and global speech delay and one had seizures and unilateral hearing loss (Table 2).

Ten of the 14 children with unfavourable outcomes had a discontinuous trace (>30s). For these 14 children, the median (range) discontinuity in seconds was 50.3 (9.6, 55.1) and 55.2 (24.8, 58.0) at 10 and 15 μV respectively at 24 hours and 18.1 (0.1, 47.7) and 42.8 (5.3, 53.3) at 48 hours (Figure 2). A mean discontinuity >30 s per 1-minute epoch has a PPV of 100% and 87% at 24 and 48 hours respectively (10 μV threshold) and of 91% and 90% at 24 and 48 hours (15 μV threshold) for unfavourable neurodevelopmental outcome (Table 3).

Of the 14 children with unfavourable clinical outcomes, 10 had MR images predictive of unfavourable outcome. Of the remaining four children, two had profound bilateral hearing loss and one had seizures and unilateral hearing loss, which the MRI system does not predict. One infant died at 6 months from complications of evolving cerebral palsy.

For the 29 children with favourable neurodevelopmental outcomes only one had EEG discontinuity >30s at both time epochs and voltage thresholds. Six of these 29 had MRIs that would predict likely neurodisability: three of these children had neurodevelopmental abnormalities including mildly impaired cognition, and/or delayed speech and language development, and three were classified as normal at the time of assessment. Overall, the correlation between MRI and neurodevelopmental outcome was good: Pearson's R=0.62 ($p<0.001$). Of the six children lost to follow-up, five had MRI predictive of favourable outcomes.

Discussion

Our study indicates that excessive EEG discontinuity assessed objectively with our automated software is associated with increased cerebral tissue injury on MRI, and is independently predictive of abnormal neurodevelopmental outcome in infants with HIE who have undergone TH. This association was statistically significant at 24 and 48 hours of age, at 10 μV and 15 μV thresholds. Using a discontinuity cut-off of 30 s, PPVs of 75-90% were obtained for MRI-inferred outcomes and even higher PPVs for neurodevelopmental outcomes. The sensitivity for adverse neurodevelopmental outcome was greatest at 24 hours at 71% whereas the specificity at this time was at least 97%. This highlights the importance of early EEG monitoring in identifying infants who are likely to benefit from therapeutic interventions.

Among infants with unfavourable MRI outcomes, the median discontinuity values dropped from 31.2 and 43.5 seconds at 24 hours to 2.7 and 20.3 s at 48 hours at 10 μV and 15 μV respectively, i.e. to below 30 s at both voltage thresholds. Hence in infants undergoing TH, the PPV of a discontinuous trace for cerebral tissue injury on MRI is greater at 24 hours than at 48 hours with a substantial number of babies with poor MRI outcomes having EEG discontinuity values less than 30 s at 48 hours. This method may provide an important tool for risk stratification in early postnatal life when adjunctive therapies are most likely to be beneficial.

In earlier work we found that high seizure burden (seizures longer than 15 minutes per hour) was associated with brain tissue injury[8], but we were unable to investigate the contribution of discontinuity, and its co-occurrence with seizure burden, to tissue injury and outcome due to technical limitations. The novel automated software we have developed for reliable quantification of discontinuity from cotside recordings of the EEG has now enabled such analysis: the evidence for collinearity between seizure burden and discontinuity was weak, which suggests that the point estimates of effect of each of these predictor variables in the model are likely to be reliable. Our novel automated software analysed single channel cross-

cerebral EEG data, therefore it could be utilised with other aEEG/EEG software from which the raw EEG data can be extracted.

Previous studies have shown a relationship between features of multichannel EEG background[17] as well as limited channel EEG/aEEG measures[18] and MRI outcomes in neonatal encephalopathy in the pre-cooling era, in that increased EEG depression is associated with more severe abnormality on cerebral MRI. Studies have shown the predictive value of EEG discontinuity lasting at least 30 s with adverse neurodevelopmental outcomes in infants with HIE[6] as well as in groups of infants with broader neurologic diagnoses[7] in the precooling era. Menache et al.[7] reported that all 10 babies (100%) with a predominant interburst interval duration of 30 s or greater had adverse neurologic outcomes; however, in that study the analogue EEG recordings may have been shorter with a minimum duration of 30 minutes. The use of automated quantification of background EEG activity has previously been demonstrated in infants[13 19]. In a qualitative multichannel video-EEG study, Nash et al.[9] found that a persistent burst suppression or continuous low voltage pattern beyond 24 hours of age in infants undergoing TH was highly predictive of brain injury on MRI. Using qualitative aEEG background patterns, a summary trend of the raw EEG, for term infants who had undergone TH, Thoresen et al.[10] showed that the PPV of an abnormal aEEG background for poor outcome in cooled infants was >90% at 24 hours in contrast to normothermic infants in whom the PPV of an abnormal trace reached 90% by age 12 hours. In the present study using an unbiased objective measure of discontinuity, we found similar PPVs at 24 and 48 hours of age in cooled babies and the PPV of the lower voltage threshold was greater.

Although our study was primarily designed to investigate the relationship between EEG discontinuity and MRI outcomes, we were also able to show an independent significant relationship between discontinuity and neurodevelopmental outcomes with a high PPV at 24 hours. We also found high concordance between MRI outcomes and later clinical outcomes at neurodevelopmental follow-up. The high early PPV of EEG discontinuity for abnormal MRI

and neurodevelopmental outcomes may be a useful tool for early stratification of asphyxiated newborn babies for potentially beneficial adjunctive neuroprotective therapies.

Acknowledgements

We are grateful to Dr Courtney Wusthoff for her assistance with rating the seizure burden. We are grateful to all the nursing and medical staff from the study sites and all the families.

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Table 1: Characteristics of study infants

Perinatal Characteristics (total neonates = 49)	
Male sex	32 (65%)
Median birth weight, grams (range)	3360 (2450-4560)
Median Apgar score at 10 min (IQR), n=44	6 (4, 8)
Median first pH, by cord or within 1h, mmol/L (IQR), n=48	6.91 (6.81, 7.10)
Median first base deficit, by cord or within 1h, mmol/L (IQR), n=46	-16.9 (-11.3, -21.5)
Need for respiratory support at 10min age	37 (76%)
Median age when heart rate first >100/min, minutes (IQR), n=48	2 (1, 5)
Median age at first gasp, minutes (range) n=41	5 (0, 20)
Antenatal sentinel event identified	8 (16%)
Suspected clinical seizures	36 (73%)
Treated with anticonvulsants	37 (76%)
Received sedation during cooling	42/46 (91%)
Median age at start of aEEG monitoring (range), n=47	4h 50m (15m to 11h 20 m)
Median duration of aEEG monitoring (range), n=48	89h 53m (13h 20m to 168h 58m)
Any seizures identified on aEEG/EEG	29 (59%)
High seizure burden on aEEG/EEG	18 (37%)
Epoch analysed at 24 and 48 hours, minutes (range)	119 (80, 120)
Median age at MRI, days (interquartile range)	11 (8, 14)
Severe pattern of injury on MRI (group 1)	17/49 (35%)
Unfavourable neurodevelopmental outcome	14/43 (33%)

Table 2: Discontinuity values in seconds, MRI, seizure burden and neurodevelopment for the study babies.

Baby	DC† 10μV at 24h	DC† 15μV at 24h	BGT	PLIC	White Matter	Seizure Burden‡	Neurodevelopmental Outcome
1	0	0	Mild	Normal	Mild	None	Normal
2	0	0	Mild	Normal	Moderate	None	Normal
3	0	0	Mild	Normal	Moderate	None	Normal
4	0	0	Mild	Normal	Normal	None	Normal
5	0	0	Mild	Normal	Mild	None	Normal
6	0	0	Mild	Normal	Normal	Low	Normal
7	0	0	Normal	Normal	Mild	Low	Normal
8	0	0	Mild	Normal	Mild	None	Normal
9	0	0	Mild	Normal	Moderate	None	Bilateral SN hearing loss
10	0	0	Normal	Normal	Normal	None	n/a
11	0	0	Normal	Normal	Normal	None	n/a
12	0	0.1	Normal	Normal	Normal	None	Normal
13	0	0.2	Mild	Normal	Normal	None	Normal
14	0	0.2	Normal	Normal	Severe	High	Normal
15	0	0.2	Mild	Normal	Moderate	High	Normal
16	0	0.2	Mild	Normal	Moderate	Low	Seizures and unilateral hearing loss
17	0	1.2	Normal	Normal	Mild	None	Normal
18	0	3.3	Moderate	Partially Impaired	Severe	High	Normal
19	0	21.5	Mild	Normal	Moderate	High	Normal
20	0.1	0.8	Moderate	Normal	Severe	High	Mild speech delay
21	0.1	1.8	Mild	Normal	Normal	None	Normal
22	0.1	12.5	Normal	Normal	Normal	None	Normal
23	0.2	1.7	Mild	Normal	Mild	None	n/a
24	0.2	3.3	Mild	Normal	Mild	High	Normal
25	0.3	18.6	Normal	Partially Impaired	Normal	None	Normal
26	0.6	3.5	Moderate	Normal	Mild	None	Normal
27	0.6	9.9	Normal	Normal	Mild	Low	Normal
28	0.9	11.1	Severe	Severely Impaired	Severe	High	Dyskinetic CP
29	1.2	8.6	Normal	Normal	Severe	High	Normal
30	2.4	16	Moderate	Normal	Moderate	None	n/a
31	2.4	18.5	Normal	Normal	Normal	Low	Bilateral SN hearing loss, significant receptive and expressive speech delay
32	2.9	9.4	Mild	Normal	Moderate	None	Normal
33	3.6	9.3	Mild	Normal	Mild	High	Normal
34	4.8	24.3	Normal	Normal	Normal	Low	n/a
35	5	19.6	Mild	Normal	Mild	High	Mild delay
36	7.4	23.3	Mild	Normal	Mild	Low	Normal
37	7.9	18.8	Moderate	Severely Impaired	Mild	None	Normal
38	25.2	47.3	Normal	Normal	Mild	Low	n/a
39	27.7	50.4	Mild	Normal	Mild	High	Normal
40	31.2	43.5	Severe	Severely Impaired	Moderate	Low	Quadriplegic CP
41	47.3	50.3	Moderate	Severely Impaired	Mild	High	Spastic quadriplegic CP, GDD, SN hearing loss and dystonia
42	49.2	54.4	Severe	Severely Impaired	Moderate	High	GDD, microcephaly, visual impairment, dystonia with epilepsy and GORD
43	51.4	56.5	Severe	Severely Impaired	Moderate	High	Quadriplegic CP
44	51.8	56	Severe	Severely Impaired	Severe	Low	Died
45	54.5	58	Moderate	Severely Impaired	Severe	High	Global speech delay, autism and seizures
46	55.3	57.9	Moderate	Severely Impaired	Moderate	High	Died
47	58.6	59.9	Severe	Severely Impaired	Moderate	Low	Died
48	58.9	59.7	Mild	Partially Impaired	Normal	High	Died
49	59.4	59.5	Severe	Severely Impaired	Moderate	High	Spastic quadriplegic CP

† DC: Discontinuity (at stated threshold and time epoch).
‡ Low seizure burden includes either no or sporadic seizures, high seizure burden includes either frequent seizures or status epilepticus.
BGT: Basal ganglia and thalami, PLIC: Posterior limb of the internal capsule, CP: Cerebral palsy, GDD: Global developmental delay, GORD: Gastro-oesophageal reflux disease. SN, sensori-neural.

Table 3: Univariable analyses for the association between risk factors and poor outcome on MRI (first grid) and multivariable regression model assessing significant factors in univariable analyses against poor MRI outcome (second grid). Predictive values for unfavourable outcome with a mean discontinuity >30s on MRI (third grid) and neurodevelopmental outcome (fourth grid).

Univariable Analysis

Independent	**χ^2 or ANOVA* Statistic**	**P Value**
Seizure Burden	8.76	0.003
Apgar 10	*F=3.13	0.084
Lowest cord or infant pH in first hour	*F=0.03	0.860
Worst base deficit in first hour	*F=1.23	0.273
Use of anticonvulsants	2.28	0.131

Binary Logistic Regression

	OR	**Lower CI**	**Upper CI**	**P Value**
Seizure Burden	4.20	1.01	17.5	0.05
10 μV at 24 hours	1.05	1.01	1.1	0.01
15 μV at 24 hours	1.04	1.01	1.1	0.01
10 μV at 48 hours	1.06	1.00	1.1	0.04
15 μV at 48 hours	1.05	1.01	1.1	0.01

Predictive Values of Discontinuity (>30s) for Unfavourable MRI Outcomes

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Area under ROC**	**P Value**
10 μV at 24 hours	53%	94%	82%	79%	0.80	0.001
15 μV at 24 hours	53%	91%	75%	78%	0.79	0.001
10 μV at 48 hours	41%	97%	87%	76%	0.78	<0.001
15 μV at 48 hours	47%	94%	80%	77%	0.81	0.001

Predictive Values of Discontinuity (>30s) for Unfavourable Neurodevelopmental Outcomes

	Sensitivity	**Specificity**	**PPV**	**NPV**	**OR**	**95%CI**
10 μV at 24 hours	71%	100%	100%	88%	-	-
15 μV at 24 hours	71%	97%	91%	88%	9.6	1.48, 62.66
10 μV at 48 hours	50%	97%	87%	80%	6.4	1.02, 40.33
15 μV at 48 hours	64%	96%	90%	85%	8.5	1.31, 54.78

OR: Odds ratio, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, ROC: Receiver operating characteristic.

Figure 1: Plots comparing mean discontinuity and MRI outcome (favourable or unfavourable). The left panels shows mean discontinuity at 24 hours and the right panels at 48 hours. The top panels utilise a 10 μV threshold and the bottom panels a 15 μV threshold. The box edges show the interquartile range and the whiskers the range.

Figure 2: Plots comparing mean discontinuity and neurodevelopmental outcome. The left panels shows mean discontinuity at 24 hours and the right panels at 48 hours. The top panels utilise a 10 μV threshold and the bottom panels a 15 μV threshold. The box edges show the interquartile range and the whiskers the range.